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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re application of: | Confirmation No.: |
| LEE *et al.* | Art Unit: To be assigned |
| Appl. No. To be assigned | Examiner: To be assigned |
| Filed: Herewith | Atty. Docket: |
| For: **Process and Methods for Controlling the Suppression of the Neoplastic Phenotype** | |

# Exhibits to Statement of Inventorship of Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee

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| LEE *et al* | Art Unit: To be assigned |
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**Declaration Under 37 C.F.R. § 1.132 of Theodore Friedmann, M.D., M.A.**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned, Theodore Friedmann, M.D., M.A. (Oxon), declares and says as follows:

1. I am currently Professor, Department of Pediatrics, and Director of the Program in Human Gene Therapy at the Center for Molecular Genetics at the University of California, San Diego ("UCSD"), in La Jolla, California, where I also serve as the Muriel Whitehill Professor of Biomedical Ethics. A copy of my curriculum vitae is attached as Exhibit A to this Declaration.

2. I have served as a Professor of Pediatrics at UCSD since July 1981, and as Director of the Human Gene Therapy Program since November 1993. In 1972, I coauthored a paper entitled "Gene therapy for human genetic disease?" which was published in the journal *Science*, and which is widely considered to be a seminal paper on human gene therapy. (*See* Exhibit B, attached.) As detailed in my curriculum vitae, I have developed extensive expertise over the years in the methods and concepts underlying human gene therapy. Since

1998, I have served as a member of the Recombinant DNA Advisory Committee of the National Institutes of Health, which is charged with evaluating all gene therapy protocols submitted to the Federal Government. I was recently appointed Chair of that Committee, a position that I will assume in December of 2001.

3. In 1987 and 1988, while employed as a Professor in the Department of Pediatrics at UCSD, I served as Principal Investigator for my own research group at the Center for Molecular Genetics. At that time, my research group was widely considered to be one of the world's foremost groups in terms of expertise and success with retroviral mediated gene transfer techniques and its applications to human gene therapy.

4. In the late Summer and early Fall of 1987, my research group had an existing collaboration with Dr. Wen-Hwa Lee's research group focusing on characterizing the structure of the human retinoblastoma susceptibility gene ("Rb"). At the time, Dr. Wen-Hwa Lee headed a research group in the Department of Pathology of the Center for Molecular Genetics, School of Medicine, University of California at San Diego, La Jolla, California. Earlier that year, Dr. Lee's group had published a paper describing the cloning, identification and sequence of the Rb gene. At that time, however, my group was the only group at UCSD that had the isoelectric focusing capabilities necessary for comprehensive characterization of gene structure. The results of our collaboration with Dr. Lee's group on Rb gene structure were published jointly by my laboratory and Dr. Lee's laboratory in 1988. (*See* Exhibit C, attached.) As the head of a research group at UCSD, I frequently discussed my group's projects and capabilities with the heads of other research groups, and vice versa. Through such discussions, and from my group's existing collaboration with Dr. Lee's group on

characterization of the Rb gene, it became clear to me that Dr. Lee's group needed my group's expertise and assistance to design and construct a retroviral vector suitable for delivering the Rb gene to tumor cells to determine its role in tumor suppression. It is my recollection that in the late Summer- Fall of 1987, Dr. Lee's group did not have the expertise or experience in designing and preparing gene transfer vectors suitable for transfecting cancer cells with the Rb cDNA. It was also apparent to me that Dr. Lee's group sought to collaborate with my group for assistance in designing and constructing an efficient and effective vector for the Rb gene because of the well-known expertise of my laboratory in the area of retroviral mediated gene transfer.

5. Of the members of my research group at that time, Dr. Jiing-Kuan Yee was most proficient at designing vector constructs. Consequently, he was assigned primary responsibility for conceiving of a design for and constructing the Rb vector. As is customary, Dr. Yee frequently reported to and consulted with me about his progress while working on this project, and made suitable changes in his strategy as needed based on our discussions. Dr. Yee was the member of my research group who was most involved with our efforts to construct a vector for Rb, and who had the most interaction with members of Dr. Lee's group on this project.

6. At the outset of our group's collaboration with Dr. Lee's group on the Rb vector project, Dr. Yee and I consulted on a strategy for designing a vector for Rb, and jointly conceived of a plan to modify our proprietary pLLRNL retroviral vector for this purpose. The pLLRNL vector was a retroviral vector that had been designed and constructed entirely in my laboratory by members of my research group prior to any collaboration with Dr. Lee's group.

At the time of our collaboration with Dr. Lee's group, it had not yet been disclosed in any published papers, and therefore it was considered proprietary to our lab.

7. In conceiving of a design for and constructing the Rb vector, our primary concern was to construct a vector capable of stable and efficient transgene expression. There are a number of factors that influence proviral stability in any given case, all of which must be taken into consideration in designing the vector. These include: vector design, the nature of the reporter and selectable marker genes, the existence of internal transcription units, the nature of the internal promoter, the presence or absence of selective pressure, and the nature of the target cell. At the time of the Rb vector project, in the late Summer-Fall of 1987, there were no universally accepted rules available to us or any other research group for the design of stable and efficiently expressing vectors. Because my laboratory was studying these factors far more actively than other laboratories, we had a greater understanding of the importance of these factors than other investigators. We realized that each specific vector needed to be custom designed and tailored to the specific gene and target cell, and our laboratory had the requisite technical expertise to custom design and construct such vectors. We published our analysis of the factors influencing vector design in 1989, after the establishment of the collaboration with Dr. Lee for the Rb vector preparation. (*See* Exhibit D, attached.)

8. My laboratory's efforts resulted in the conception of and construction of a novel vector, pLRbRNL, which contained the Rb gene. Based on our previous experiences and ongoing studies with the proprietary pLRRNL vector and other vector constructs, we determined that placing the transgene under the control of the 5' LTR and the use of the RSV promoter as an internal promoter to drive the Neo gene expression seemed to be an optimal

design. Although other arrangements of the vector components were possible, we selected our final version based on ongoing studies in our laboratory of how retroviral vector design influences transgene stability and expression. Specifically, we knew from these studies that some of the arrangements resulted in unstable constructs or insufficient levels of expression, and that not only the nature of the gene but the precise arrangement of the vector components can greatly effect long term stability and expression. A copy of that paper is attached as Exhibit E.

9. After our group conceived of and constructed the pLRbRNL vector, we gave it to Dr. Lee's group to test in cancer cells. Using the same pLRbRNL vector that our group had conceived of and constructed for them, Dr. Lee's group successfully introduced the cloned Rb gene into retinoblastoma and osteosarcoma cells that had inactivated endogenous Rb genes and showed that expression of the exogenous Rb gene affected cell morphology, growth rate, soft agar colony formation, and tumorigenicity. This is believed to be the first ever demonstration of suppression of the neoplastic phenotype by a single gene, and the findings were the subject of a paper published in the journal *Science* on December 16, 1988, on which I am listed as an author along with Dr. Yee and members of Dr. Lee's group.

10. The contents of that paper, including the details concerning our conception of the design for and construction of the pLRbRNL vector, were subsequently incorporated substantially *verbatim* into a U.S. patent application filed on behalf of The Regents of the University of California and naming as inventors Dr. Wen-Hwa Lee and certain other members of his group. Neither Dr. Yee nor I were consulted regarding the preparation or filing of the patent application, nor were we listed as inventors. In fact, we were never told

by Dr. Lee of the filing of this application, and only became aware of it much later in conversations with representatives of the University of California.

11. It was not until 2000, when Dr. Yee and I decided that it was necessary to retain our own counsel, that we were able to conclude, with our counsel's aid, that an error in inventorship had occurred due to the fact that we were not named as coinventors on the originally filed application.

12. The undersigned further declares that all statements made herein of his knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements or the like so made are punishable by fine, imprisonment, or both under § 1001 of Title 18, United States Code, and that such willful false statements may jeopardize the validity of any application or patent issued thereon.

30 Nov. 2001
Date

Theodore Friedmann
Theodore Friedmann, M.D., M.A. (Oxon)

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